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<p>(54) Title: METHODS FOR TREATING IMPLANTABLE BIOLOGICAL TISSUES TO MITIGATE THE CALCIFICATION THEREOF AND BIOPROSTHETIC ARTICLES TREATED BY SUCH METHODS</p> <p>(57) Abstract</p> <p>A method for treating fixed biological tissue inhibits calcification of the biological tissue following implantation thereof in a mammalian body. The method includes placing the biological tissue in contact with glutaraldehyde and then heating the glutaraldehyde. Alternatively, methods other than heating (e.g., chemical or mechanical means), for effecting polymerization of the glutaraldehyde may also be utilized. Alternatively, the tissue may be heat treated prior to fixing thereof. Alternatively, methods other than glutaraldehyde may also be used for fixing the tissue. The biological tissue may be so treated at any time prior to implantation thereof in a mammalian body.</p>			
<pre> graph TD A[10 HARVEST TISSUE FROM ANIMAL OR HUMAN CADAVER] --> B[12 RINSE TISSUE IN SALINE SOLUTION FOR 1-6 HOURS] B --> C1[14 FIX TISSUE USING 0.625% GLUTARALDEHYDE SOLUTION AT ROOM TEMPERATURE FOR AT LEAST THREE HOURS] B --> C2[13 FIX AND HEAT TREAT TISSUE IN 0.625% GLUTARALDEHYDE AT 35-55°C FOR 4-22 WEEKS] B --> C3[17 HEAT TREAT IN SALINE] C1 --> D[15 HEAT TREAT TISSUE IN 0.625% GLUTARALDEHYDE AT 35-55°C FOR 4-22 WEEKS] C3 --> D D --> E[16 STERILIZE WITH ALCOHOL/FORMALDEHYDE SOLUTION FOR TWO HOURS AT ROOM TEMPERATURE] E --> F[18 PERFORM ANTIMINERALIZATION; OPTIONALLY SIMULTANEOUSLY HEAT TREAT] F --> G[20 TRIM TISSUE AND ADD OPTIONAL NON-BIOLOGICAL COMPONENTS, e.g., VALVE HOLDER] G --> H[22 STERILIZE IN ALCOHOL/FORMALDEHYDE SOLUTION FOR NINE HOURS AT 34-38°C] H --> I[24 STORE TISSUE IN GLUTARALDEHYDE AT ROOM TEMPERATURE] </pre>			

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METHODS FOR TREATING IMPLANTABLE BIOLOGICAL TISSUES TO
MITIGATE THE CALCIFICATION THEREOF AND BIOPROSTHETIC
ARTICLES TREATED BY SUCH METHODS

Field of the Invention

5 The present invention pertains generally to biomedical materials, and more particularly to preserved biological tissues, such as porcine bioprosthetic heart valves, which are implantable in a mammalian body.

10 Background of the Invention

The prior art has included numerous methods for preserving or fixing biological tissues, to enable such tissues to be subsequently implanted into mammalian bodies. Examples of the types of biological tissues 15 which have heretofore been utilized for surgical implantation include cardiac valves, vascular tissue, skin, dura mater, pericardium, ligaments and tendons.

The term "grafting" as used herein is defined as the implanting or transplanting of any living tissue or organ 20 (See Dorlands Illustrated Medical Dictionary, 27th Edition, W.B. Saunders Co. 1988). Biological tissues which are grafted into the body of a mammal may be xenogeneic (i.e., a xenograft) or allogeneic (i.e., an allograft).

25 The term "bioprostheses" defines many types of biological tissues chemically pretreated before implantation (Carpentier - See Lonescu (editor), Biological Tissue in Heart Valve Replacement, Butterworths, 1972). As opposed to a graft, the fate of 30 a bioprostheses is based upon the stability of the chemically treated biological material and not upon cell viability or host cell ingrowth. Chemical pretreatment

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includes the "fixing" or tanning of the biological tissue. Such fixing or tanning of the tissue is accomplished by exposing the tissue to one or more chemical compounds capable of cross-linking molecules 5 within the tissue.

Various chemical compounds have been utilized to fix or cross-link biological tissues including formaldehyde, glutaraldehyde, dialdehyde starch, hexamethylene diisocyanate and certain polyepoxy compounds.

10 In particular, glutaraldehyde has proven to be relatively physiologically inert and suitable for fixing various biological tissues for subsequent surgical implantation (Carpentier, A., J. Thorac. Cardiovasc. Surg. 58:467-68 (1969)). In particular, examples of the 15 types of biological tissues which have heretofore been subjected to glutaraldehyde fixation include porcine bioprosthetic heart valves and bovine pericardial tissues.

Clinical experience has revealed that 20 glutaraldehyde-fixed bioprosthetic tissues may tend to become calcified. Such calcification of glutaraldehyde-fixed bioprosthetic tissues has been reported to occur most predominantly in pediatric patients see, Carpentier et al. and "Continuing Improvements in Valvular 25 Bioprostheses, J. Thorac Cardiovasc. Surg. 83:27-42, 1982. Such calcification is undesirable in that it may result in deterioration of the mechanical properties of the tissue and/or tissue failure. In view of this, surgeons have opted to implant mechanical cardio-vascular 30 valves into pediatric patients, rather than to utilize glutaraldehyde-preserved porcine valves. However, pediatric patients who receive mechanical valve implants require long term treatment with anticoagulant medications and such anticoagulation is associated with 35 increased risk of hemorrhage.

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The mechanism by which calcification occurs in glutaraldehyde-fixed bioprosthetic tissue has not been fully elucidated. However, factors which have been thought to influence the rate of calcification include:

- 5 a) patient's age
 - b) existing metabolic disorders (i.e.,
 hypercalcemia, diabetes, kidney failure
 ...)
 - 10 c) dietary factors
 - d) race
 - e) infection
 - f) parenteral calcium administration
 - g) dehydration
 - h) distortion/mechanical factors
 - 15 i) inadequate coagulation therapy during
 initial period following surgical
 implantation; and
 - j) host tissue chemistry
- 20 Various efforts have been undertaken to find ways of mitigating calcification of glutaraldehyde fixed bioprosthetic tissue. Included among these calcification mitigation techniques are the methods described in U.S. Patent No. 4,885,005 (Nashef et al.) SURFACTANT TREATMENT
25 OF IMPLANTABLE BIOLOGICAL TISSUE TO INHIBIT CALCIFICATION; U.S. Patent No. 4,648,881 (Carpentier et al.) IMPLANTABLE BIOLOGICAL TISSUE AND PROCESS FOR PREPARATION THEREOF; U.S. Patent No. 4,976,733 (Girardot) PREVENTION OF PROSTHESIS CALCIFICATION; U.S. Patent No.
30 4,120,649 (Schechter) TRANSPLANTS; U.S. Patent No. 5,002,2566 (Carpentier) CALCIFICATION MITIGATION OF BIOPROSTHETIC IMPLANTS; EP 103947A2 (Pollock et al.) METHOD FOR INHIBITING MINERALIZATION OF NATURAL TISSUE DURING IMPLANTATION and WO84/01879 (Nashef et al.)

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SURFACTANT TREATMENT OF IMPLANTABLE BIOLOGICAL TISSUE TO
INHIBIT CALCIFICATION.

There remains a need for the development of new methods for inhibiting or mitigating calcification of 5 chemically-fixed biological tissue.

It is postulated that tissue calcification may be minimized by accelerating the polymerization of glutaraldehyde solution coming into contact with the tissue prior to implantation.

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Summary of the Invention

The present invention specifically addresses and alleviates the above-mentioned deficiencies associated 15 with the prior art. More particularly, the present invention comprises a method for treating glutaraldehyde fixed biological tissue or biological tissue fixed with other chemicals so as to inhibit later calcification of the tissue following implantation of the tissue into a 20 mammalian body. The method comprises placing the biological tissue in contact with glutaraldehyde or another chemical fixative and then heating the glutaraldehyde or other fixative and/or causing the glutaraldehyde or other fixative to be polymerized by 25 thermal, chemical or mechanical means.

In the preferred embodiment of the present invention the biological tissue is disposed within a container containing a 0.625% solution of glutaraldehyde comprising approximately 26 ml/l glutaraldehyde (25%); approximately 30 4.863 g/l HEPES buffer; approximately 2.65 g/l $MgCl_2 \cdot 6H_2O$; and approximately 4.71 g/l NaCl. The balance of the solution comprises double filtered H_2O . Sufficient NaOH is added to adjust the pH to approximately 7.4.

The glutaraldehyde solution is heated to between 35 approximately 35-55°C for approximately 4-22 weeks.

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The biological tissue may be heat treated any time prior to implantation thereof within a mammalian body. For example, the tissue may be treated before fixing thereof. Treatment before fixing of the biological tissue merely involves heating it in a saline solution (9 g/l NaCl) or any other physiologic solution at 25-80°C for a few seconds to 22 weeks. Alternatively, the tissue may be treated during fixing thereof, while the tissue is disposed within a glutaraldehyde solution. Treatment during fixing of the biological tissue merely involves heating of the glutaraldehyde solution to approximately 25-80°C for approximately a few seconds to several months. The preferred range is 35 to 55°C for 4-22 weeks.

Alternatively, the biological tissue is treated after fixing thereof, and before storage thereof. Such treatment is preferably accomplished while the biological tissue remains within the glutaraldehyde solution utilized during the fixing process and/or is disposed with a glutaraldehyde solution within which the biological tissue is to be stored and again merely comprises heating of the glutaraldehyde solution to approximately 25-80°C for approximately 4-22 weeks.

Alternatively, the biological tissue is treated after storage thereof, typically a short time prior to implantation within a mammalian body. The biological tissue is preferably heated within the glutaraldehyde solution within which it has been stored by merely heating the glutaraldehyde solution to approximately 35-55°C for approximately 4-22 weeks.

Alternatively, the biological tissue is treated during an antimineralization process by adding glutaraldehyde to the antimineralization solution and heating, preferably to approximately 35-55°C for approximately 4-22 weeks. As those skilled in the art

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will recognize, various antimineratization processes are utilized to inhibit mineralization of the biological tissue by calcium and various other minerals.

Heating of the glutaraldehyde appears to effect 5 polymerization thereof. It is believed that the inhibition of calcification is due to the polymerization of glutaraldehyde contained within the biological tissue. As such, those skilled in the art will appreciate that 10 various other cross linking agents and other processes, such as light, radiation, or chemicals, which effect polymerization of glutaraldehyde may likewise be utilized in the method for treating biological tissue of the present invention. Thus, various chemical fixatives other than glutaraldehyde and other methods for effecting 15 polymerization of these chemicals and/or glutaraldehyde may be used alone, or in combination with heat, so as to effect polymerization of the chemicals contained within the biological tissue, thereby inhibiting later calcification of the tissue after implantation thereof in 20 a mammalian body.

The method of inhibiting calcification of fixed biological tissue may be utilized with various different types of biological tissue such as cardiac valves, 25 vascular tissue, skin, dura mater, pericardium, fascias, ligaments, and tendons. Those skilled in the art will realize that this list is not comprehensive in that various other types of biological tissue may also benefit from treatment thereof according to the method of the present invention.

These, as well as other advantages of the present invention will be more apparent from the following description and drawings. It is understood that changes in the specific structure shown and the described may be made within the scope of the claims without departing 35 from the spirit of the invention.

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Brief Description of the Drawings

Figure 1 is a flow diagram illustrating the prior art process for preparing biological tissue for implantation within a mammalian body comprising fixing of 5 the biological tissue with a glutaraldehyde solution; and

Figure 2 is a flow chart of the preparation of biological tissue for implantation in a mammalian body comprising the method for inhibiting calcification of the 10 biological tissue according to the present invention.

Detailed Description of the Preferred Embodiment

The detailed description set forth below in connection with the appended drawings is intended as a 15 description of the presently preferred embodiment of the invention, and is not intended to represent the only form in which the present invention may be constructed or utilized. The description sets forth the functions and sequence of steps for constructing and operating the 20 invention in connection with the illustrated embodiment. It is to be understood, however, that the same or equivalent functions and sequences may be accomplished by different embodiments that are also intended to be encompassed within the spirit and scope of the invention.

25 The method for treating glutaraldehyde fixed biological tissue to inhibit calcification thereof following implantation in a mammalian body is illustrated in Figure 2 which depicts a flow chart of the presently preferred embodiment of the invention. Figure 1 depicts 30 a flow chart of the prior art method for preparing biological tissue for implantation within a mammalian body.

Referring now to Figure 1, the prior art process for preparing biological tissue for implantation within a 35 mammalian body comprises first harvesting the tissue from

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an animal or human cadaver (10). As those skilled in the art will recognize, various different types of tissue are routinely harvested from different animals and/or human cadavers. For example, heart valves are routinely harvested from pigs, pericardium is routinely harvested from cows or pigs, and skin is routinely harvested from human cadavers. Those skilled in the art will further recognize that new tissues are, from time to time, being found to be implantable within a mammalian body.

5 10 After harvesting, the biological tissue is rinsed in saline solution, typically for a period of 1-6 hours (12).

The tissue is next fixed using a 0.65% glutaraldehyde solution at room temperature for at least 15 3 hours (14). As is well known, glutaraldehyde effects cross-linking of the proteins, e.g., collagen, within the tissue. Such cross-linking tends to make the tissue more durable and effects preservation thereof. It is known that cross-linked protein exhibits increased resistance 20 to proteolytic cleavage and further that one of the major processes by which circulating blood may destroy tissue is via enzymatic activity which involves unfolding of the protein substrate in order to facilitate enzymatic hydrolysis. Cross-linking of the protein of a tissue 25 makes the tissue resistant to such unfolding, and consequently tends to prevent deterioration thereof due to the enzymatic activity of blood.

The tissue is next sterilized, preferably with an alcohol/formaldehyde solution for 2 hours at room 30 temperature (16). The preferred solution for effecting sterilization of the tissue comprises approximately 12 ml/l of Tween 80; approximately 2.65 gms/l of MgCl₂ · (H₂O; approximately 108 ml/l of formaldehyde (37%); approximately 220 ml/l of ethyl alcohol (100%) and 35 approximately 4.863 gms/l of HEPES buffer. The balance

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of the solution comprises double filtered H₂O. The pH of the solution is typically adjusted to 7.4 via the addition of NaOH. Those skilled in the art will recognize various other sterilization solutions are 5 likewise suitable.

Antimineralization treatment (18) is optionally performed so as to inhibit the accumulation of mineral deposits upon the biological tissue after implantation of a mammalian body. As those skilled in the art will 10 recognize, various different antimineratization treatments are utilized so as to prevent the deposition of various different minerals upon the biological tissue.

The tissue is trimmed and any non-biological components are then added thereto (20). For example, it 15 is common to sew a heart valve to a valve holder which aids in the handling thereof and which may additionally function as a mount for the valve when implanted into a mammalian body.

Next, the biological tissue is once again sterilized 20 (22), preferably in an alcohol/formaldehyde solution as discussed above. Since preparation of the biological tissue is substantially complete and the biological tissue will next likely be stored for an extended period of time, a more rigorous sterilization procedure from 25 that previously utilized is typically employed. At this stage, the biological tissue is typically sterilized for approximately 9 hours at 34-38°C.

After sterilization, the biological tissue is stored in glutaraldehyde at room temperature (24).

30 Referring now to Figure 2, the method for treating glutaraldehyde fixed biological tissue to inhibit calcification thereof following implantation in a mammalian body comprises the additional step of heating preferably when the glutaraldehyde is in contact with

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the biological tissue, to approximately 35-55°C for approximately 4-22 weeks.

Heating of the biological tissue may be performed at any time after harvesting the tissue from the animal or 5 human cadaver and prior to implanting the tissue within a mammalian body. However, heating of the biological tissue is preferably performed at a point in the process for preparing the biological tissue when the biological tissue is already disposed within a bath of 10 glutaraldehyde solution, as occurs at various stages of the process according to the prior art. Thus, the method for treating glutaraldehyde fixed biological tissues according to the present invention is preferably performed either during fixing thereof with a 15 glutaraldehyde solution, immediately after fixing thereof with the glutaraldehyde solution, or alternatively just prior to or after being stored in a glutaraldehyde solution.

As a further alternative, the method for treating 20 glutaraldehyde fixed biological tissues may be performed during antimineralization treatment by adding glutaraldehyde to the antimineralization solution and heating the solution, preferably to approximately 35-55°C for approximately 4-22 weeks.

25 For example, after fixing tissue using a 0.625% glutaraldehyde solution at room temperature for at least 3 hours (14), the biological tissue may be heat treated in either the same or different 0.625% glutaraldehyde solution, preferably at approximately 35-55°C for 30 approximately 4-22 weeks (15).

As one of the alternatives discussed above, the biological tissue is fixed and heat treated simultaneously (13) in the 0.625% glutaraldehyde solution, again preferably at approximately 35-55°C for

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approximately 4-22 weeks. Another alternative is to heat the tissue in saline (17) prior to fixation (21).

As the other alternative discussed above, the biological tissue may simultaneously undergo antimineralization treatment and heat treatment (19).
5 Glutaraldehyde is added to the antimineralization solution so as to effect the inhibition of calcification of the tissue following implantation in a mammalian body.

Thus, the method for treating fixed biological
10 tissue so as to inhibit calcification thereof following implantation in a mammalian body tends to substantially increase the usable life of such tissue subsequent to implantation in a mammalian body, thereby mitigating the requirement for subsequent tissue replacement. As those
15 skilled in the art will appreciate, such tissue replacement frequently causes substantial trauma to the patient, occasionally resulting in the patient's death. As such, it is greatly beneficial to be able to either avoid or postpone the need for the replacement of
20 implanted biological tissue.

It is understood that the exemplary method for treating glutaraldehyde fixed biological tissue described herein and shown in the drawings represents only a presently preferred embodiment of the present invention.
25 Indeed, various modifications and additions may be made to such embodiment without departing from the spirit and scope of the invention. For example, various fixing agents, such as aldehydes other than glutaraldehyde, may exhibit properties similar to those of glutaraldehyde so
30 as to make them suitable for use in the present invention and, thus, may likewise be utilized. Accordingly, these and other modifications and additions may be obvious to those skilled in the art and may be implemented to adapt
35 the present invention for use in a variety of different applications.

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WHAT IS CLAIMED IS:

1. A method for treating glutaraldehyde fixed biological tissue to inhibit calcification of said tissue following implantation in a mammalian body, said method comprising the steps of:
 - a) placing the biological tissue in contact with glutaraldehyde; and
 - b) heating the glutaraldehyde.
2. The method as recited in Claim 1 wherein the step of placing the biological tissue in contact with glutaraldehyde comprises placing the biological tissue in contact with an approximately 0.625 % solution of glutaraldehyde comprising:
 - a) approximately 26 ml/l glutaraldehyde (25%);
 - b) approximately 4.863 g/l HEPES buffer;
 - c) approximately 2.65 g/l MgCl₂ • 6H₂O;
 - d) approximately 4.71 g/l NaCl;
 - e) balance of solution double filtered H₂O;
 - and
 - f) sufficient NaOH to adjust pH to approximately 7.4.
3. The method as recited in Claim 1 wherein the step of heating the glutaraldehyde comprises heating said solution of glutaraldehyde to approximately 35-55°C.
4. The method as recited in Claim 1 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde for approximately 4-22 weeks.
5. The method as recited in Claim 1 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde during the process of fixing the biological tissue.
6. The method as recited in Claim 1 wherein the step of heating the glutaraldehyde comprises heating said

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glutaraldehyde after fixing of the biological tissue and before storage of the biological tissue.

7. The method as recited in Claim 1 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde after storage of the biological tissue.

8. The method as recited in Claim 6 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde in which the biological tissue is subsequently stored.

10 9. The method as recited in Claim 1 wherein the biological tissue is stored in a glutaraldehyde solution after fixation of the tissue has been completed and wherein the step of heating the solution of glutaraldehyde comprises heating the solution of glutaraldehyde in which the biological tissue is stored.

15 10. The method as recited in Claim 1 wherein the tissue is treated, after fixation treatment with an antimineratization treatment solution containing glutaraldehyde, and wherein the step of heating the glutaraldehyde comprises heating glutaraldehyde containing antimineratization treatment solution with which said tissue is treated.

20 11. A method for treating glutaraldehyde fixed biological tissue to inhibit calcification following implantation in a mammalian body, the method comprising the steps of:

- a) disposing the biological tissue in a solution of glutaraldehyde; and
- b) causing the glutaraldehyde to polymerize.

25 12. The method of Claim 11 wherein step (b) comprises applying heat to cause said glutaraldehyde to polymerize.

30 13. The method of Claim 11 wherein step (b) comprises adding a chemical to the glutaraldehyde to cause the glutaraldehyde to polymerize.

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14. The method of Claim 11 wherein step (b) comprises utilizing mechanical means to cause the glutaraldehyde to polymerize.

15. The method as recited in Claim 11 wherein the 5 step of disposing the biological tissue in a solution of glutaraldehyde comprises dispensing the biological tissue in an approximately 0.625 % solution of glutaraldehyde comprising:

10 a) approximately 26 ml/l glutaraldehyde (25%);

b) approximately 4.863 g/l HEPES buffer;

c) approximately 2.65 g/l MgCl₂ • 6H₂O;

d) approximately 4.71 g/l NaCl;

e) balance of solution double filtered H₂O;

15 and

f) sufficient NaOH to adjust pH to approximately 7.4.

16. A bioprostheses formed by the process of Claim

1.

20 17. The bioprostheses of Claim 16 wherein the fixed biological tissue comprises:

a) a cardiac valve;

b) vascular tissue;

c) skin;

25 d) dura mater;

e) pericardium;

f) a ligament; and/or

g) a tendon.

18. The bioprostheses of Claim 16 wherein the step 30 of heating the glutaraldehyde comprises heating said glutaraldehyde during fixing of the biological tissue.

19. The bioprostheses of Claim 16 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde after fixing of the biological tissue and 35 before storage of the biological tissue.

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20. The bioprosthesis of Claim 16 wherein the step of heating the glutaraldehyde comprises heating said glutaraldehyde after storage of the biological tissue.

21. The bioprosthesis of Claim 16 wherein the step 5 of heating the glutaraldehyde comprises heating glutaraldehyde containing antimineralization solution with which said tissue is treated.

22. A bioprosthesis formed by the process of Claim 11.

10 23. The bioprosthesis of Claim 22 wherein the fixed biological tissue comprises:

- a) a cardiac valve;
- b) vascular tissue;
- c) skin;
- 15 d) dura mater;
- e) pericardium;
- f) a ligament; and/or
- g) a tendon.

24. The bioprosthesis of Claim 22 wherein the step 20 of causing the glutaraldehyde to polymerize comprises heating said glutaraldehyde.

25. The bioprosthesis of Claim 22 wherein the step of causing the glutaraldehyde to polymerize is carried out during fixing of the biological tissue and before 25 storage of the bioprosthesis.

26. The bioprosthesis of Claim 22 wherein the step of causing the glutaraldehyde to polymerize is carried out after fixation but prior to bioprosthesis.

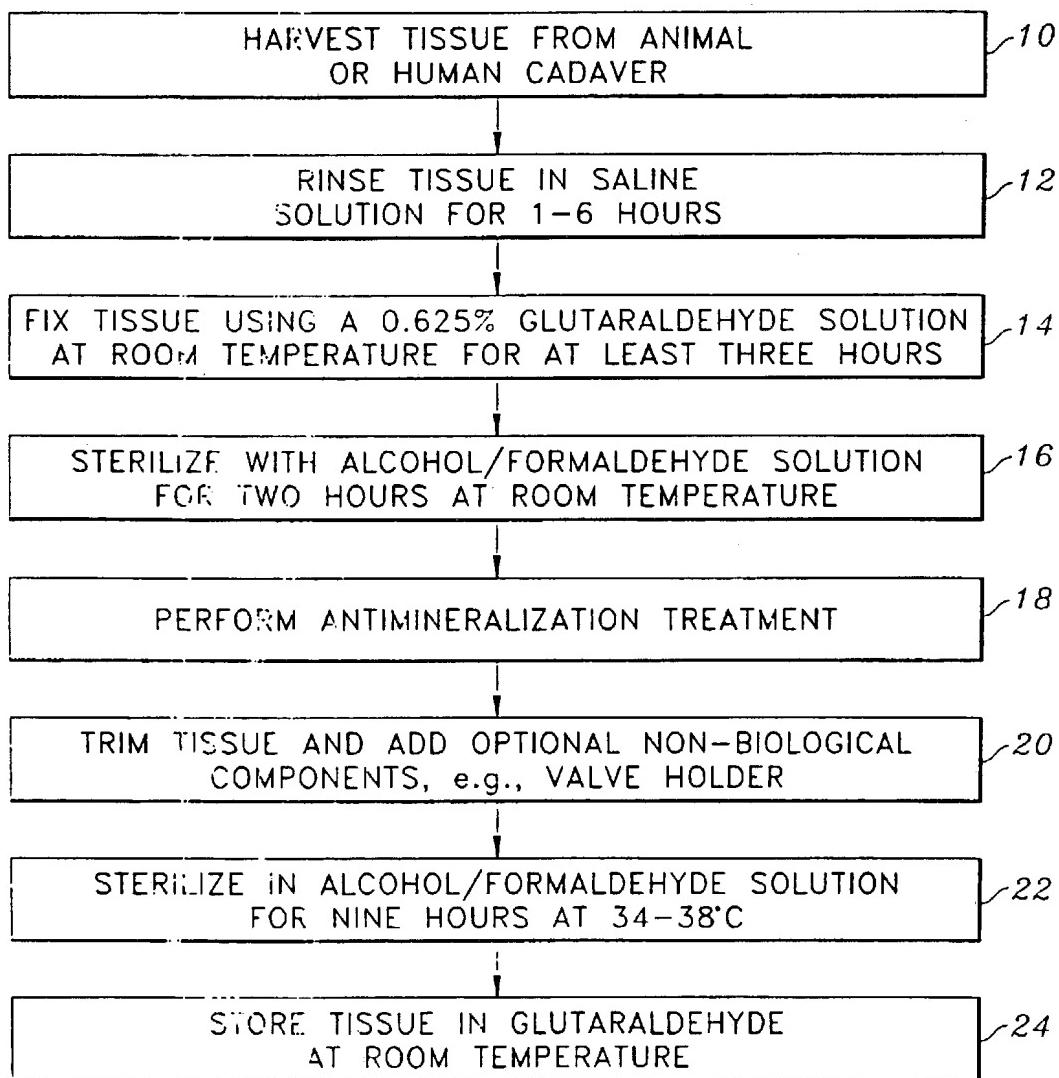
27. The bioprosthesis of Claim 22 wherein the step 30 of causing the glutaraldehyde to polymerize is carried out concomitantly with exposure of the bioprosthesis to a glutaraldehyde containing antimineralization treatment solution.

28. The bioprosthesis of Claim 22 wherein the step 35 of causing the glutaraldehyde to polymerize is carried

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out after fixation and during storage of the bioprosthesis in a glutaraldehyde - containing storage solution.

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(PRIOR ART)

FIG. 1

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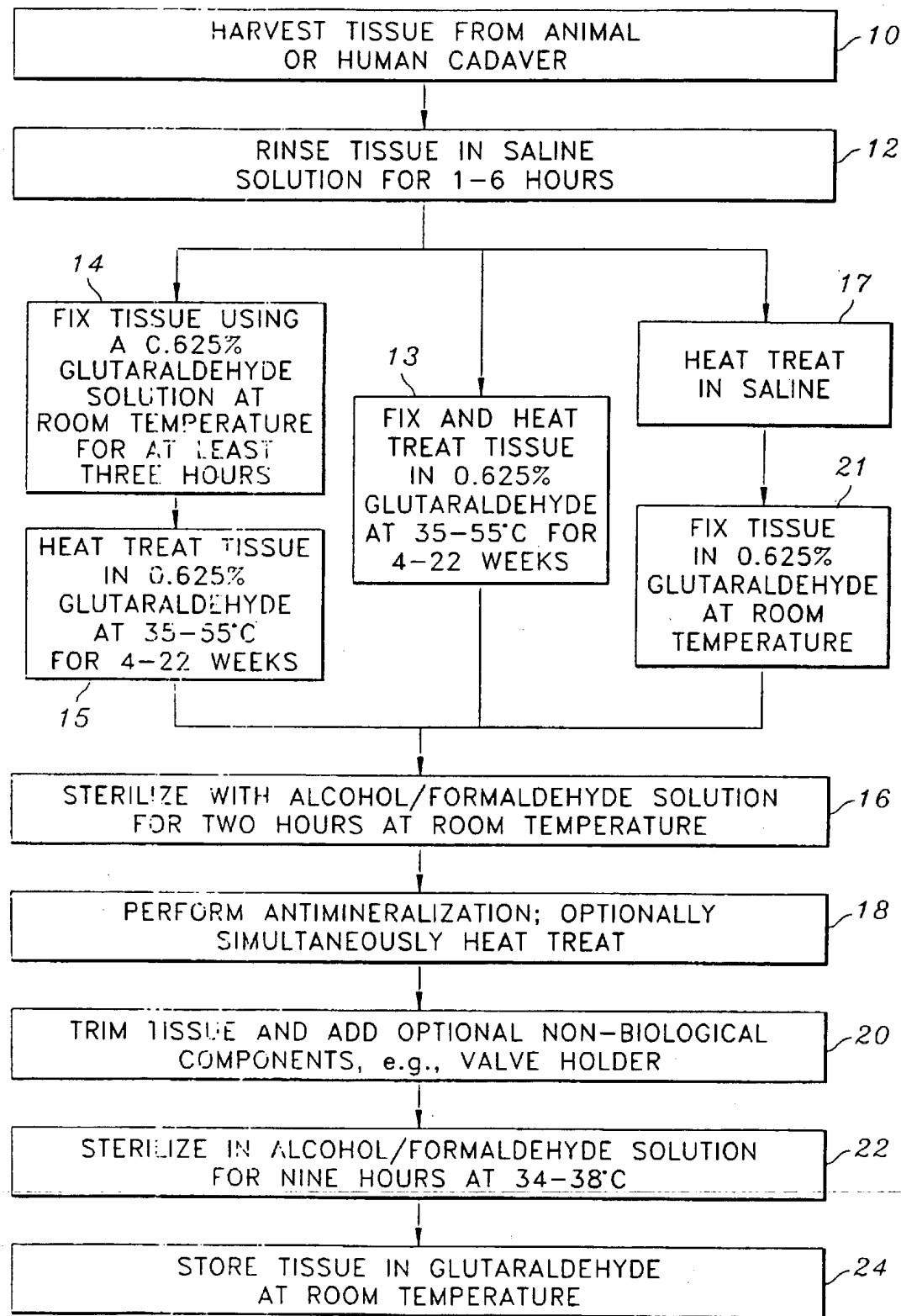


FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/10001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9219 Derwent Publications Ltd., London, GB; AN 92-157549 & SU,A,1 651 890 (CARDIO-VASCUL SURGY) , 23 May 1991 see abstract --- US,A,4 402 697 (POLLOCK E.M.) 6 September 1983 see column 5, line 22 - line 24; claim 1 --- WO,A,84 01894 (AMERICAN HOSPITAL SUPPLY) 24 May 1984 see page 5, line 21; claims 1,7,15 ---	1,4,6, 11,12, 16,17, 19, 22-24,26
X		1,3,6, 11,12, 16,17, 19, 22-24,26
X		1,3,16, 17
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

31 October 1995

Date of mailing of the international search report

29.12.95

Name and mailing address of the ISA

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Peltre, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/10001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 770 665 (NASHEF A.S.) 13 September 1988 ---	
A	WO,A,93 19209 (SEIFTER E.) 30 September 1993 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/10001

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US-A-4770665	13-09-88	NONE		
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